



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/812,382	03/20/2001	Ashutosh Chilkoti	4176-101	1286

23448 7590 10/01/2003

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
RESEARCH TRIANGLE PARK, NC 27709

EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
----------	--------------

1652

DATE MAILED: 10/01/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/812,382

Applicant(s)

CHILKOTI, ASHUTOSH

Examiner

Malgorzata A. Walicka

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-10,12-19,21-28,31,32,62-72,74-76 and 78-85 is/are pending in the application.
- 4a) Of the above claim(s) 62-65 and 83-85 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-10,12-19,21-28,31,32,66-72,74-76 and 78-82 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☒ The proposed drawing correction filed on 23 June 2003 is: a) ☒ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

Art Unit: 1652

The Amendment of June 23, 2003, filed as paper No. 15 is acknowledged. Amendments to the claims have been entered as requested. Claims 1, 8, 12, 17-19, 27, 31, 71, 72 and 74 are amended; claim 77 is cancelled. New claims 78-85 are added. Claims 1, 3-10, 12-19, 21-28, 31-32, 62-72, 74-76 and 78-85 are pending. Claims 1, 3-10, 12-19, 21-28, 31-32, 66-72, 74-76 and 78-82 are the subject of this Office Action. Claims 62-65 and 83-85 are withdrawn from consideration as directed to non-elected invention.

DETAILED ACTION

1. Election/Restriction

In their Remarks, Applicants noted that in connection with prospective rejoinder they added new method claims 82-85. Claim 82 is inadvertently categorized as a method claim. The claim is directed to a fusion protein.

Upon finding claim(s) of Group I directed to an allowable product, pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claim 62 and 63-65, and new claims 82-85 directed to the processes of using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, will be rejoined and fully examined for patentability under 37 CFR 1.104.

2. Objections

2.1. Drawings

Newly submitted submitted Fig. 3 is accepted by examiner.

3. Rejections

3.1. 35 USC section 112, second paragraph

Rejection withdrawal

Claims 1-7, 25-26 and 31 were rejected in the previous Office Action, paper no. 13. This rejection of claims 1-7, 25-26 and 31 is now withdrawn, because the term "protein" as defined by Applicants on page 9, line 7, encompasses polypeptides of any length.

Rejection of claim 8 made in the previous Office Action, paper No. 13 is withdrawn, because the claim has been amended.

Rejection of claim 17-19 made in the previous Office Action because the term ELP was used in claims in two meanings, is now withdrawn, because the claims have been amended.

Rejection of claim 72 for lack of antecedents is withdrawn, because claim 71 has been amended.

Rejection of claim 76 is withdrawn, because Applicants arguments are found persuasive.

Rejection of claim 77 is moot because the claim has been cancelled.

Rejections caused by amendment

Amended claim 71 remains rejected, because the term "an ELP component" is not defined by the claims or specification rendering the claim indefinite.

Art Unit: 1652

Claim 1 and dependent claims 3-10, 12-19, 21-26, 66-70 are rejected because claim 1 recites the limitation "wherein the insoluble phase of the fusion protein is of sufficient mass to be centrifugally removed from a solution."

Firstly, the mass of the insoluble phase in a solution depends on the concentration of the fusion protein in this solution. Thus, the limitation is the property of the concentration and not the intrinsic property of the fusion protein. Secondly, absent a quotation of centrifugation conditions, particularly a centrifugation force, the claim is unclear, because practically any protein can be centrifugally removed from a solution when the appropriate centrifugation force is provided.

New rejection

Claim 8 is rejected for reciting the phrase "some ...of its transition character". The phrase "some of its transition character" is indefinite, because the disclosure fails to define the scope of the phrase. It is unknown what the term transition character means and it is unknown what the term some defines. The term some is a relative term which renders claim 8 indefinite. The term "some" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Claims 74 and 75 are confusing. The claims are directed to a fusion protein comprising the cleavable site in a composition containing an agent capable to cleave said cleavable site. When the composition contains the cleaving agent, the composition

Art Unit: 1652

cannot comprise the fusion protein as claimed in base claim 72, because said fusion protein will be destroyed by the cleaving agent.

3.2. 35 USC section 112, first paragraph

3.2.1. Lack of written description

Claims 1, 3-10, 12-19, 21-28, 31-32, 66-77 and 78-82 are rejected under 35 U.S.C. 112, first paragraph for the reasons stated in the previous Office Action, paper No. 10 and 13, and reiterated below.

The claims are directed to a fusion protein exhibiting a phase transition, comprising one or more peptides or proteins (a), one or more proteins exhibiting inverse phase transition (b) and a spacer (c) wherein the fusion protein retains the inverse Phase transition behavior of the phase transition protein and wherein the insoluble phase of the fusion protein is of sufficient mass to be centrifugally removed from a solution. Thus, the claims are directed to large and variable genus of fusion proteins exhibiting a phase transition.

Regarding part a) of the fusion protein, neither the claims nor the specification set forth the limitation for structure of proteins of part (a) and neither the claims nor the specification do particularly point out which features of said proteins ensure the capacity of exhibiting the phase transition of the fused protein the part of which said proteins are going to be. The specification teaches two species of the genus, thioredoxin and tendamistat, small molecules containing 108 and 74 amino acids. The specification does not disclose any limitation on the structure of proteins that may be used instead of

Art Unit: 1652

thioredoxin and tendamistat. Thus the disclosure teachings are not sufficient for identifying the features of all proteins that are able to support the capacity of exhibiting the phase transition.

In their remarks Applicants write:

"For a chemical genus, the written description requirement may be satisfied if a 'representative number of species' are sufficiently described by disclosure of relevant identifying characteristics, such as physical or chemical properties, or functional characteristics" (page 17, 3rd line from the bottom, and page 18, the first line).

This argument of Applicants have been fully considered but is found unpersuasive. The specification teaches two species of the genus, thioredoxin and tendamistat, small molecules containing 108 and 74 amino acids. These two polypeptides cannot be considered to be representative number of species of the enormous genus of proteins and polypeptides, because they do not allow for identification of the genus by basic biochemical chemical characteristics such as:

- 1) primary, secondary and tertiary structure,
- 2) molecular weigh,
- 3) electric charge,
- 4) viscosity,
- 5) biologic function.

In their response, page 7, line 26 Applicants state, "The ELP tag can be attached to **any peptide or protein** [emphasis added] of interest to form the ELP-tagged fusion protein of the present invention wherein the ELP-tagged fusion protein exhibits an inverse phase transition."

Applicants' argument has been fully considered but is found not persuasive. For example, it is doubtful that large proteins, with molecular weight higher than 100,000 Da, exhibiting a large positive charge, are good candidates for part (a) of the claimed fusion protein.

Regarding part b) of the fusion protein, claims 1, 3-10, 12-19, 21-28, 31-32, 66-77 and 78-82 are also rejected because they are generic and do not set forth the sequences of the phase transition protein (b) that are to be used for constructing the fusion protein. The genus of the phase transition proteins is a large genus, for which the specification fails to give sufficient structural description. The Applicants disclose the fusion proteins in which part (b) is a peptide or protein comprising up to 90 units of pentapeptides Val-Pro-Gly-X-Gly, wherein X is any natural or artificial amino acid except for proline. The specification also teaches the possibility of use of pentapeptide IPGXG. It is however not disclosed that use of up to 90 repeats of this pentapeptide will have the same effect as that of Val-Pro-Gly-X-Gly. These pentapeptides or peptides consisting of them, are species that do not identify the structure of all elastin-like polypeptides.

Regarding the spacer, part c) of the fusion protein, it is identified only by referring to the types of protease that can be used to its cleavage, i.e, thrombin and in general, serine, cysteine, aspartyl, metalloproteases could be used. Again the structures that can be

Art Unit: 1652

used as spacers and cleaved by said enzymes are species of enormous genus for which the specification lacks further identifying structural characteristics.

In conclusion, description of fusion proteins is insufficient to identify all elastine like fusion proteins as encompass by the scope of the claims. Applicants did not provide sufficient identifying structural characteristics of the claimed invention so that one skilled in the art was convinced that at the time the application was filed, Applicants had possession of the claimed invention.

Claim 9, 66-72, and 74-75 are rejected because neither the claim nor the specification describe the phase transition of the claimed fusion protein wherein the phase transition is mediated by changing pH, addition of solutes and/or solvents, side chain ionization, chemical modification, and changing pressure. The disclosure set forth the phase transition induced by changes of the temperature, when other conditions are constant. The disclosure teaches how changes in NaCl concentration would change the transition temperature, however it is not clear how the change in NaCl itself would induce phase transition. The disclosure is silent of other solutes. Therefore, because claims are lacking written description of changing pH, addition of solutes and/or solvents, side chain ionization, chemical modification, and changing pressure, wherein these changes cause phase transition, one skilled in the art is not convinced the inventors were in possession of the claimed invention at the time the application was filed.

Art Unit: 1652

Traversing the rejection under 35 USC section 112 first paragraph, Applicants write, (Remarks, page 20, line 13),

"The art of phase transition proteins exhibiting an inverse transition was well known at the time the present application was filed, and is adequately disclosed in the specification (see disclosure, page 13, lines 17-20 and page 14, page 13-14). At pages 13-14 of the instant disclosure, applicant describes the use of the VPGXG pentapeptide, as well as the IPGXG pentapeptide. Additionally, applicant directs the reader of the instant application to International Patent Application PCT/US96/05186¹⁰ for examples of additional suitable phase transition polypeptides, and such international patent application further directs the reader to U.S. Patent Nos. 4,783,523, 4,870,055, 4,898,926, and U.S. Serial No.08/24,874, now U.S. Patent No. 5,527,610. Each of these references thoroughly describes elastin-like polypeptides that exhibit an inverse phase transition."

Applicant's arguments have been fully considered but are found not persuasive for the following reasons.

Art Unit: 1652

A. Pages 13-14 present information related to the phase transition proteins that consists of the basic pentapeptides set forth by VPGXG, as well as the IPGXG. Applicants, however disclose a fusion protein consisting of three parts, a), b) and c), wherein part b) comprises up to 90 repeats of VPGXG pentapeptide. Applicants also suggests use of the IPGXG, however Applicants do not themselves have constructed a protein comprising IPGXG.

B. The fact that "Each of these references thoroughly describes elastin-like polypeptides that exhibit an inverse phase transition." does not mean that each of these elastin-like polypeptides was used by Applicants as part (b) of their fusion proteins. Applicant's invention does not contain any "elastin-like polypeptide", but up to 90 repeats of VPGXG or IPGXG.

Furthermore the Applicant contends,

"It would be within the ability of one skilled in the art, giving the high level of knowledge and expertise in the general field of the instant invention, and the guidance and direction of the instant invention, to prepare fusion proteins comprising elastin like-polypeptides (ELPs), and using ELPs that were known and available at the time of filling the present invention, including those ELPs described in International Patent Application PCT/US96/05186, and U.S. Patent Nos.

Art Unit: 1652

4,783,523, 4,870,055, 4,898,926, and U.S. Serial No.08/246,874,
now U.S. Patent No. 5,527,610"(Remarks, page 20, line 22).

The examiner agrees that high level of knowledge and expertise in the general field of the instant invention enables one skilled in the art to prepare fusion proteins comprising elastin like-polypeptides. For that reason the claims should define what is included and excluded from the scope of the claimed invention, i.e. what was reduced to practice by inventors.

Taking into account lack of written description of structures of the species of the genus of proteins of part (a), (b), c) it is concludes that the inventors were not in possession of the claimed invention at the time the application was filed.

In summary, claims 1, 3-10, 12, 13-19, 27-28, 31-32, 66-72 and 74-76 are rejected because one skilled in the art is convinced that at the time the application was filed, **Applicants had no possession** of the claimed invention.

3.3. 35 USC, section 102

Rejection of claim 1, 4, 6, 21, 25, 26, 27, 28, 31, made in the previous Office Action, paper No 13, over under McPherson et al. (Production and Purification of a Recombinant Elastomeric Polypeptide, G-(VPGVG)₁₉-VPGV, from *Escherichia coli*, Biotechnol. Prog. (1992), 8, 347-352, is withdrawn because the claims have been amended.

Art Unit: 1652

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.


If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner



PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600